3297 '99 AUG -4 P2:16

August 4, 1999

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 97N-0314/CP3
Supplement to Citizen Petition on
Scheduling and Procedure

In its September 25, 1998 Citizen Petition on Scheduling and Procedure, Knoll Pharmaceutical Company ("Knoll" or "KPC") asked that FDA allow adequate time for Knoll to supplement and FDA to review the company's December 15, 1997 Citizen Petition, 97N-0314/CP2, asserting that Synthroid levothyroxine sodium tablets are generally recognized as safe and effective ("GRAS/E Citizen Petition") before the date on which an NDA would have to be submitted as a practical matter to meet the August 2000 deadline originally imposed by the August, 1997 Federal Register notice (the "Notice").[1] Knoll urged FDA to revise its schedule so that NDAs would not have to be submitted until at least 6 months after FDA rules on Knoll's GRAS/E Citizen Petition and at least 6 months after FDA rules on the request in the Scheduling and Procedure Citizen Petition for clarification of its procedures. Knoll also asked FDA to confirm that the agency would allow Knoll at least 60 days after Knoll has received a complete response to its September 12, 1997 Freedom of Information Act request to submit a supplement to its GRAS/E Citizen Petition. Finally, Knoll asked FDA to resolve important procedural issues by declaring that it will treat all applications received pursuant to the Notice as NDAs, not ANDAs.

Several recent developments and FDA's continuing failure to respond to Knoll's September 12, 1997 FOIA request make even more imperative FDA's favorable response to Knoll's Citizen Petition on Scheduling and Procedure.

1. Prescription Drug Products: Levothyroxine Sodium, 62 Fed. Reg. 43535.

97N-0314

SUP2

1. Bioavailability Issues

The Notice specified that a bioavailability study would be required as part of any NDA for levothyroxine sodium products. As stated in its GRAS/E Citizen Petition, Knoll believes that Synthroid is not a new drug and that no NDA is required for it. If, however, Knoll ultimately must submit an NDA, then it will have to submit a bioavailability study.

FDA has just recently issued its draft guidance on bioavailability.[2] Comments are not due until August 9, and it will doubtless take FDA some time thereafter to publish its final guidance. What the final outcome will be seems very much in doubt, for the draft guidance adopts a methodology for levothyroxine bioavailability which the agency had previously criticized as flawed and unsuitable when Knoll used it in certain promotional materials. Moreover, this 180 degree reversal on FDA's part was unknown to Knoll, although it was known to at least one of its competitors in the second half of 1997 or January 1998.[3]

As a result of this belated publication of a draft bioavailability guidance, the fact that it represents a complete departure from FDA's previous position, and the resulting need for Knoll (and perhaps other companies as well) to reconsider their approach to bioavailabity and the possible need for additional or different studies, submission of an NDA by the August, 1999 date needed to give FDA one year before the August 2000 date set by the Notice becomes more problematic than it had been. For that reason alone, it makes sense to build some additional time into the schedule.

2. FOIA Issues

FDA has still not produced a complete response to Knoll's September, 1997 FOIA request. Although Knoll is preparing a supplement to its GRAS/E Citizen Petition utilizing the documents it has received so far, it believes there are many more relevant documents which FDA is required to produce but has not, as set forth in Knoll's July 29, 1999 FOIA update.[4] In addition, although FDA promised in October, 1998 to advise the company in the near future whether it would deny Knoll's requests for certain documents, it has not yet provided either the

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2. Draft Guidance for Industry on In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets, Docket No. 99D-1149, 64 Fed. Reg. 31280 (June 10, 1999).

3. See Knoll's comments on the draft guidance, Letter from Nancy L. Buc to Dockets Management Branch, August 2, 1999 (copy attached).

4. Letter from Nancy L. Buc and Gary L. Veron to Roy V. Castle, Jr., M.S., P.D. (copy attached (exhibits omitted)).

documents or a denial. Without the documents, Knoll cannot know whether a further supplement is in order, and without a denial, it cannot appeal the agency's decision not to provide the documents.[5]

For these reasons, Knoll reiterates its request that the agency confirm that Knoll will have at least 60 days after FDA completes its response to its FOIA request to supplement its GRAS/E Citizen Petition. See Citizen Petition on Scheduling and Procedure, Request 2, page 4.

3. Procedural Issues

In its Scheduling and Procedure Citizen Petition, Knoll stated that it had learned from a letter to the docket that FDA might be considering approval of at least one or more ANDAs rather than NDAs. See pages 3 and 8 and footnote 7. In an FOIA response dated April 20, 1999, FDA provided documents confirming that at least some FDA employees are considering just that. In the cover letter, however, FDA said:

> Some of the responses provided during the meeting as documented in the minutes may not reflect current Center for Drug Evaluation and Research (CDER) policy regarding the handling of levothyroxine applications. We are in the process of reexaming the questions posed by Jones and will provide clarification of CDER's position to Jones, and to Knoll, and other interested parties, as soon as possible.[6]

Knoll has not yet received any such clarification. Knoll does not know whether the issues FDA is reexamining are the same issues as those it presented in the procedural section of its Scheduling and Procedure Petition nor how FDA means to decide these issues. Thus, FDA's cover letter only confuses further the issues which Knoll requested the agency to resolve. In light of this additional uncertainty, Knoll renews its request for a declaration that the procedure set forth in the Notice is the procedure FDA will use, and that it will not use any other procedure. See Citizen Petition on Scheduling and Procedure, Request 3, page 4.

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5. Knoll could treat the failure to either produce or deny as a denial and institute litigation under the Freedom of Information Act, but it continues to prefer to try to resolve these issues directly with the agency.

6. Letter from Carolann W. Hooton to Nancy L. Buc, Apr. 20, 1999 (copy attached).

Conclusion

For those additional reasons, as well as those stated in its Citizen Petition, Knoll asks that its Citizen Petition on Scheduling and Procedures be granted.

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